Remarks

The Office Action mailed June 24, 2010 has been received and reviewed. Claims 1-14, 16, and 18-33 are pending, of which claims 3-14 are withdrawn from consideration, leaving claims 1, 2, 16, and 18-33 as pending and under examination. Claim 1 is amended. Applicants respectfully request that the rejections be reconsidered and withdrawn in view the remarks that follow.

Claim Amendments

Claim 1 is amended to correct informalities. No new matter is introduced by the amendments.

The 35 U.S.C. §103 Rejection

Claims 1, 2, 16, and 18-33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Publication No. 2003-0139364 A1 (Krieg), in view of U.S. Patent No. 5,573,781 (Brown) and International Patent Publication No. WO 1996/029394 (Granger). Applicants respectfully traverse.

Claim 1 is independent. Each of claims 2, 16, and 18-33 depends from claim 1 and therefore includes all of the features recited in claim 1. Thus, remarks that refer to claim 1 apply equally to each of claims 2, 16, and 18-33.

Applicants respectfully submit that the combination of Krieg, Brown, and Granger (collectively, "the suggested combination of documents") fails to establish a *prima facie* case of obviousness against claim 1. M.P.E.P. §2141(III) states:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. (emphases added).

Applicants respectfully submit that the Office Action has failed to meet its burden to provide a clear articulation of reasons, based on sound scientific principles, why the subject matter of claim 1 would have been obvious to one skilled in the art from the combined teachings of Krieg, Brown, and Granger. Each of the rationales A-G for supporting a rejection under 35 U.S.C. §103 includes being able to reach a predictable result upon making the suggested combination ((C) "in the same way" implies predictability). Rationale (G) is the teaching, suggestion, motivation test, which must be coupled with a reasonable expectation of success in order to establish a *prima facie* case of obviousness. M.P.E.P. §2143.02. Any reasonable expectation of success is dependent upon there being sufficient predictability in the art on which the expectation can be founded. Thus, each rationale set forth by M.P.E.P. §2141 for supporting a rejection under 35 U.S.C. §103 requires, expressly or implicitly, that the suggested combination of documents provides sufficient teaching that one skilled in the art at the time the invention was made would have been able to predictably obtain the claimed subject matter.

Claim 1 recites, generally, a method that includes depositing within a tumor an IRM depot preparation that provides an extended residence time within the localized tumor tissue.

Krieg discloses administering certain IRM compounds, including resiquimod, in combination with cancer vaccines that induce a subject's immune system to mount an immune response against a tumor. Krieg also discloses various forms of administration for doing so. The Office has acknowledged that Krieg fails to disclose resiquimod for the treatment of breast cancer as a preferred embodiment or depositing resiquimod in a localized tissue. (Office Action dated July 31, 2008, page 7).

Brown is cited for teaching direct delivery of anti-cancer agents into a tumor mass to limit exposure to surrounding normal tissue. The Office acknowledges that Brown fails to teach administering resiquimod or the co-administration of a vaccine. (Office Action dated October 16, 2009, page 3).

Granger is said to teach administering mixed lymphocytes within a tumor site to increase immunogenic reaction and thereby reduce tumor size and asserts that the mixed lymphocyte preparation may be considered to be a vaccine, "given that the cells are removed from a patient, modified, and then re-injected into the tumor (pg 21 Example I, section 4, alloactivation of patient mononuclear cells with donor leukocytes)." (*Id.*, page 4). Granger is further said to teach intra-tumor administration of the therapy in order to minimize risk associated with systemic delivery. (*Id.*)

The Office Action asserts that it would have been obvious, when practicing the method of Krieg to administer the composition within the tumor to maximize exposure to the tumor, and to use a vaccine product as taught in Granger "given the teaching it reduces tumor size by also inducing an immune response." (*Id.*). Applicants respectfully disagree.

Applicants respectfully submit that the interpretation of Granger is mistaken and that one skilled in the art, with a proper understanding of Granger, would not have been able to predictably practice the methods recited in claim 1 with a reasonable expectation of success.

While Granger teaches, in a superficial sense, treating a tumor by producing an immune response, the immune response generated in Granger is not the type of immune response that would be influenced by the presence of an IRM compound such as resiquimod. Consequently, Granger does not cure the acknowledged deficiencies of the combination of Krieg and Brown.

Resiquimod does not have any direct anti-tumor activity, but works indirectly to stimulate an endogenous immune response – i.e., an immune response by cells of the affected organism's immune system – against foreign antigens. In a typical immune response, foreign antigens are recognized and processed by certain immune cells, which ultimately results in a humoral (e.g., circulating antibody) immune response and/or a cellular (e.g., cytotoxic T cell) immune response against cells that express the foreign antigens. Resiquimod primes this process by activating, among other cells, the antigen presenting cells that initially phagocytize and process the foreign antigen. Thus, resiquimod helps an affected organism – e.g., in the instant claims, an organism afflicted with a tumor – mount an endogenous immune response against cells that express the foreign antigens, e.g., cells of the tumor.

Krieg teaches that compounds such as resiquimod can improve antigen-specific endogenous humoral and cell-mediated immune responses. (Krieg, paragraphs [0304]-[0306]). Those of ordinary skill in the art understand the effect of resiquimod influences an endogenous immune response is, in part, due to its mechanism of action. The antigen-specific nature of the endogenous immune response results from co-activation of antigen presenting cells by an antigen and resiquimod. Both resiquimod and the antigen are necessary to induce an antigen-specific response by the immune cell. Krieg proposes facilitating this mechanism of action by administering both the antigen and the IRM compound (e.g., resiquimod) to a subject receiving the treatment.

In contrast, Granger teaches activating allogeneic cells *in vitro*, then administering the already-activated allogeneic cells to induce a host-versus-graft response, a response which is unlike that disclosed in Krieg because it is (a) not endogenous and (b) not specific to tumor antigens. Moreover, the host-versus-graft response of Granger is not influenced by the presence or absence of an IRM compound administered to the subject. The response is not endogenous because it is not a response of the subject's own immune system. Instead, the subject's immune cells are used to activate the allogeneic cells – in effect, as the "foreign antigen" for the activation of the allogeneic cells – and induce allogeneic cells cytotoxicity against any of the subject's cells. The allogeneic cytotoxic response is not tumor antigen-specific because, as just

indicated, the allogeneic cells are primed to recognize any of the subject's cells as a target for the allogeneic cells' cytotoxic activity. To the extent that the allogeneic cells target tumor cells, they do so because the tumor cells are derived from the subject's own somatic cells and continue to express the subject's somatic cell antigens, not because the allogeneic cells specifically target tumor antigens. Finally, the allogeneic cells are not influenced by the presence or absence of IRM compounds because the allogeneic cells administered to the subject are already immunoactivated.

As noted above, the Office acknowledges that Krieg fails to disclose depositing resiquimod in a localized tissue. One reason for this failure, at least with respect to tumors, was explained in Applicants' previous response. "[M]any cancers have a microenvironment that effectively evades the immune system[.]" (Amendment and Response filed March 16, 2010, pages 7-8).

The Examiner considers Applicants' previous remarks nonpersuasive. First, the Office Action asserts that the motivation to combine the documents is not based on the mechanism of activity, but on the desire to administer the IRMs described in Krieg in a manner that maximizes tumor cell exposure while minimizing exposure to surrounding tissue. (Office Action, pages 2-3). However, differences in the mechanisms of activity are not trivial as they illuminate precisely why a person skilled in the art would not have made the suggested combination of documents. Applicants do not dispute that the technical ability to deliver IRMs to a tumor existed prior to Applicants' disclosure. Instead, prior to Applicants' disclosure, there was no reason that one of ordinary skill in the art would have reasonably predicted that doing so would provide any therapeutic benefit once one properly considered, at a minimum, the mechanism by which IRMs exert their influence on a subject's immune system in combination and the tumor microenvironment with respect to a subject's immune system.

Depositing an immune response modifier compound such as resiquimod into a tumor mass – i.e., into a tissue that evades the endogenous immune system – would be expected to be an exercise in futility because the resiquimod would be expected to be effectively sequestered from the endogenous immune cell population on which it exerts its immunostimulatory

influence. In other words, modifying Krieg to administer an IRM compound into a tumor mass defeats the purpose of the IRM compound by severely reducing the availability of the IRM compound to contact antigen presenting cells being activated by contact with tumor antigens.

Furthermore, no one of skill in the art would combine the teaching of Krieg and Granger because the IRM compounds would have no effect on the allogeneic cells of Granger. Krieg teaches activating a subject's own immune system to induce an endogenous anti-tumor immune response. As noted above, Granger teaches activating allogeneic cells *in vitro*, then administering the already-activated allogeneic cells to induce a host-versus-graft response, a response which is (a) not endogenous, (b) not specific to tumor antigens, and (c) not influenced by the presence or absence of an IRM compound.

The Examiner speculates that adding lymphocytes as taught by Granger will cause a reduction in tumor size and, as the tumor is reduced, IRM would become exposed. (Office Action, page 3). This view presupposes, without support, that the lymphocytes in Granger are effective to reduce the tumor sufficiently to cause a release of IRM compound administered within the tumor mass. Given the general unsuitability of allogeneic therapy for the treatment of solid tumors, the Examiner's unsupported speculation has no merit.

Second, the Examiner asserts that Applicants have failed to provide a basis for why a skilled person would not administer an IRM compound directly into a tumor, "given there would reasonably be expected to be some leakage which would contact the surrounding environment causing the desired immune response." (*Id.*). This is incorrect. Applicants have consistently maintained that a skilled person would not expect administering an IRM into a tumor mass to work because doing so administers the IRM to an environment that typically evades the endogenous immune system and is out of proximity to the cells of the endogenous immune system whose activity is influenced by the IRM compound. Moreover, the Examiner provides no basis for the position that a skilled person would reasonable expect "leakage" of the IRM, an unsubstantiated position that necessarily presumes that the invention – deposition of an IRM within a localized tissue region – is unsuitable for it intended purpose.

Finally, the Examiner asserts again that "the release of IRM from the tumor as it decreases will cause the immune system to recognize the tumor and cause the desired response." (*Id.*). First, this position again presupposes that the allogeneic cells of Granger are effective to reduce the tumor sufficiently to cause a release of IRM compound administered within the tumor mass. Second, there is no teaching in the combination of Krieg, Brown, and Granger that the free release of IRM in the vicinity of a tumor provides any therapeutic effect. Thus, given the known mechanism by which IRM compounds influence endogenous antigen-specific immune responses, it is unclear how one of ordinary skill in the art would expect that free release of an IRM compound such as resiquimod from a tumor would result in a tumor antigen-specific endogenous immune response.

Applicants respectfully submit that claims 1, 2, 16, and 18-33 are patentable under 35 U.S.C. §103(a) over the combination of Krieg, Brown, and Granger and therefore respectfully request that the rejection be reconsidered and withdrawn.

Request for Rejoinder

Applicants respectfully request that claims 3-14 be rejoined under M.P.E.P. §821.04(a) as depending from claim 1, an allowable elected base claim, "or otherwise require all the limitations of an allowable claim."

Summary

It is respectfully submitted that the pending claims 1-14, 16, and 18-33 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

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The undersigned hereby certifies that this paper is being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with 37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to the Commissioner for Patents, Mail Stop **RCE**, P.O. Box 1450, Alexandria, VA 22313-1450, on this 25th day of October, 2010.

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